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Evaluation of Novel Nonlaser Light Source for Endometrial Ablation Using 5-Aminolevulinic Acid

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Background and Objective: **This research evaluated the effectiveness of a new nonlaser prototype short-arc lamp to achieve photodynamic ablation of endometrium in a rat.**
Study Design/Materials and Methods: **Thirty female Sprague-Dawley rats were divided into two groups. 5-Aminolevulinic acid (ALA), the precursor to the photosensitizer protoporphyrin IX, was injected into the left uterine horn and vehicle alone (Hyskon) was injected into the right horn of 23 rats (group 1). An additional seven rats received vehicle only into both uterine horns (group 2). Three hours later, a cylindrical diffusing optical fiber was inserted into the lumen of the uterine horns, and light treatment was delivered from either a laser or a nonlaser light source. Rats in group 1 received either 1 hour (n = 15) or 10 minutes (n = 8) of light treatment into both uterine horns. In rats in group 2, the left horn was exposed to 1 hour of light treatment. Uterine tissues were examined histologically 4 days after light treatment.**
Results: **One hour of light exposure to the uterine horns injected with ALA produced extensive necrosis of the rat uterine wall. No difference in the magnitude of destruction was seen between the groups treated with the laser and nonlaser light sources. Ten minutes of light exposure resulted in endometrial ablation that was comparable in both the laser- and the prototype-treated groups, but the destruction of the deepest layers of the uterine wall was more consistent in the group treated with the nonlaser prototype. One hour of light treatment from either light source did not result in any histological changes in the uterine horns not exposed to ALA.**
Conclusion: **The extent of endometrial ablation in the rat uterine horn achieved with the nonlaser prototype was comparable to that achieved with the laser. Thus, the nonlaser prototype may provide a less expensive approach to photodynamic endometrial ablation. Lasers Surg. Med. 25:315–322, 1999.**

Key words: light sources, noncoherent, nonlaser, photodynamic therapy, uterus

INTRODUCTION

Light-activated processes are finding wide usage in medical treatments, an example being the treatment of lesions with photodynamic therapy (PDT) [1,2]. PDT involves the systemic or

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topical application of a photosensitizer that is selectively retained in the tissue to be removed, followed by light activation of the photosensitizer that destroys the tissue by the formation of highly reactive oxygen species [3]. Several visible and near infrared (IR) absorbing photosensitizers have been assessed during the past two decades [4]. One of the most novel developments in this area has been the use of 5-aminolevulinic acid (ALA), a precursor in the heme biosynthetic pathway. Topical or systemic administration of ALA causes the endogenous formation of a transient excess of protoporphyrin IX (PpIX), a potent photosensitizer [5]. Although ALA-PDT was developed primarily for oncological applications [6], it is currently being investigated for use in other areas [7,8], including gynecology [9]. Considerable attention has been focused on the possible use of ALA-PDT as a minimally invasive alternative to hysterectomy for women with menorrhagia. Menorrhagia, or uncontrolled benign uterine bleeding, brings approximately 4% of women of reproductive age to their physician for consultation on an annual basis [10]. Menorrhagia has been treated medically with oral contraceptives, cyclic or continuous progestin therapy, danazol, or medical suppression with gonadotropin-releasing hormone agonists. Each of these medications may be associated with significant expense and side effects. Furthermore, these medical treatments often provide only temporary relief, and many women will ultimately submit to hysterectomy to achieve a more permanent solution [11]. There are 700,000 hysterectomies performed each year in North America, and it is estimated that approximately 40% is for the treatment of menorrhagia [12]. Hysteroscopic endometrial ablation using laser or gynecologic resectoscopes, a newer approach to the treatment of menorrhagia, is a technically difficult procedure and has been associated with a variety of complications [13,14]. Clearly, a technique that would ensure complete endometrial destruction without the need for anesthesia and surgical intervention would be superior.

In principle, any light source that is capable of exciting a photosensitizer sufficiently could be used in PDT. In practice, however, specific types of light sources are preferred, depending on the particular details of the application. Coherent (laser) light sources are required for applications where small optical fibers (<1 mm in diameter) are used to deliver the light to the application site, such as deep inside a lesion. For certain internal sites that can be reached by large (>2 mm in diameter) fibers or light guides, noncoherent sources (such as stabilized arc lamps) become more convenient to use, primarily because of their ease of use and reduced cost. For the illumination of large surface areas, such as in many dermatological applications, laser sources become quite impractical, and conventional incandescent light sources can be suitably adapted.

Several noncoherent light sources, specifically designed for use in PDT, have recently been proposed for clinical applications [15–20]. The spectral output properties of noncoherent light sources should be tailored, as much as possible, to the absorption properties of the photosensitizer being used with extraneous wavelengths filtered out. In particular, to render any applied light doses quantitative and meaningful, there should be no "hidden" infrared component in such light sources [21]. This last issue becomes significant because of the difficulty of filtering the 1,150–2,000-nm IR component by the use of conventional filters [22]. Such IR can be removed from visible sources by the use of reflective optics, an approach often seen in the design of solar simulators [23]. We report on the use of such a custom-designed lamp as a more economical alternative to laser for the potential gynecological application, ALA-PDT ablation of endometrium. The current study compares the degree of endometrial ablation in a rat model achieved with the use of a coherent versus a noncoherent light source.

MATERIALS AND METHODS

Animals

Thirty mature (200–250 g) female Sprague-Dawley rats (Charles River, Canadian Breeding Farm and Laboratories, Montreal, QC, Canada) were maintained in temperature-controlled (24°C) quarters with free access to food (Rodent Laboratory Chow, Purina Mills Inc., St. Louis, MO) and water. A 14-hour light and 10-hour dark cycle was maintained, with the light cycle starting at 0600 hours. All experiments were approved by the Queen's University Animal Use Committee and adhered to the guidelines of the Canadian Council on Animal Care.

Light Sources

The noncoherent proprietary lamp system, designed and manufactured by Sciencetech, Inc. (London, ON, Canada), is composed of a lamp

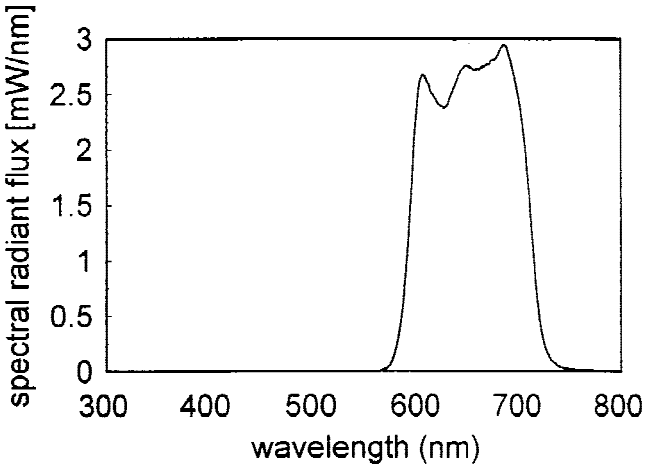

Fig. 1. Spectral distribution of light from the prototype lamp.

housing and power supply unit. The lamp housing is water cooled and incorporates a high-power short-arc Xenon bulb (1 kW), gold-plated reflector, and a fiber coupler. Dichroic reflectance optics assure the total elimination of any IR components. The fiber coupler includes a set of filters to select the wavelengths in the spectral band of 600–700 nm and a set of lenses to focus the light beam into an optical fiber (plastic, diameter = 2 mm with a 15-mm long cylindrical diffusing tip; Rare Earth Medical, Inc., Yarmouth, MA). The output of the nonlaser prototype light source was determined by using a modification of a locally developed lamp analysis system. Water pressure (cooling water) of the lamp was 25 psi, and voltage was set at 850 V. The total output power of a 2-mm-diameter bare fiber was (500 ± 20 mW) measured with a calorimetric detector (Sciencetech, Inc.). The spectral radiant flux of the light source is shown in Figure 1. The power output of the diffusing fiber tip was measured with an integrating sphere (Labsphere, North Sutton, NH) coupled to a spectral irradiance measurement apparatus [20] as opposed to the bare fiber whose total output power was known. The diffusing fiber tip showed an output power that was 0.56 ± 0.05 of the bare fiber tip output. Hence, the total output of the diffusing fiber was calculated to be 280 ± 40 mW.

The coherent light source was a frequency-doubled KTP pumped Dye Laser (Laserscope, San Jose, CA) that emitted light at 630 nm and up to 3 W of power at the fiber coupler. The total power emitted from the diffusing end of the fiber was 300 mW, as measured by the integrating sphere of the laser system Dye Module.

ALA Applications

Crystallized ALA hydrochloride (DUSA Pharmaceuticals Inc., Valhala, NY) was diluted to 10 mg/0.1 ml in Hyskon (dextran 70) immediately before administration. Rats were anesthetized with an intraperitoneal injection of a mixture containing ketamine, xylazine, acepromazine, and sterile water (volume ratio 5:5:2:8; 1 ml/kg). A 2.5-cm midline incision was then made through the abdominal wall. ALA (0.1 ml) was injected into the uterine horn with a 1-ml tuberculin syringe with a 25-gauge needle approximately 0.5 cm above the uterine bifurcation. Animals were divided into two groups: experimental (n = 23) and control (n = 7). In the experimental animals, the left horn was injected with ALA and the right horn was injected with an equal volume of vehicle (Hyskon). Animals in the control group received an injection of 0.1 ml of vehicle into both uterine horns. The abdomen was then closed, and rats were allowed to recover from the anesthetic.

Light Delivery

Three hours after ALA administration, all rats were anesthetized with 2% isoflurane. The abdominal incision was reopened, and the diffusing tip of the optical fiber was inserted into the uterine lumen through a 1.5-mm incision made in the left uterine horn, slightly above the site of ALA injection. Due to the radius of the fiber (2 mm), the uterine cavity was slightly distended and the endometrial surface was fully in contact with the surface of the diffuser. A 60-min (incident fluence = 1,080 J/cm^2) or 10-minute (incident fluence = 180 J/cm^2) treatment was initiated from either the laser or the prototype nonlaser light source.

Fifteen rats from the experimental group received 1 hour of light exposure first in the left uterine horn (ALA treated) and then in the right horn (vehicle treated). Seven rats were exposed to the light provided by the PDT laser system, and eight animals were exposed to the light from the nonlaser prototype arc lamp. The left horn of eight remaining experimental animals was exposed to 10 min of light treatment from the laser system (n = 4) or from the nonlaser prototype light source (n = 4). To control for potential damage caused by fiber insertion, the fiber was inserted into the right horn but no light was delivered.

The animals from the control group received 1 hour of light exposure in the left horn from the

laser (n = 2) or from the prototype (n = 5) light source. The fiber was inserted into the right horn but no light treatment was delivered.

Hyperthermia Monitoring

Monitoring of the uterine temperature was performed during the 1-hour light treatments (incident fluence = 1,080 J/cm^2) in photosensitized horns exposed to laser light (n = 4) or nonlaser prototype light irradiation (n = 5) and in five nonphotosensitized horns exposed to light from the prototype lamp. A thermocouple (Cole Parmer, Vernon Hills, IL) was placed inside the uterine horn and positioned between the diffuser of the optic fiber and the overlying uterine tissue.

Specimen Collection

Four days after light treatment, rats were placed into a carbon dioxide chamber and killed. A 2-cm segment from both uterine horns was removed and placed into 10% buffered formalin. The segment was cut into six pieces, embedded in paraffin wax, sectioned transversely at 3 μm, and stained with hematoxylin–eosin.

RESULTS

Histology

Uterine histology was assessed based on the following criteria: (a) absence of luminal epithelium, (b) presence of endometrial glands and status of glandular epithelium, (c) presence of stromal edema, and (d) integrity (no edema and no necrosis) of the circular and outer myometrial layers.

One hour of light exposure from either light source to the ALA-treated uterine horns resulted in extensive histologic damage to all layers of the uterine wall. Specifically, in all specimens, luminal epithelium was absent, stromal edema was prominent, and endometrial glands were absent or devoid of glandular epithelium. In addition, all specimens showed damage to the circular myometrium and focal necrosis throughout the longitudinal outer layer of myometrium. There was no difference in the extent of damage caused by laser light and the nonlaser prototype light source (Fig. 2).

In contrast, the right (vehicle treated) uterine horn of the same animals also exposed to 1 hour of laser or nonlaser prototype light showed variable results. In the noncoherent (prototype) lamp treatment group, the majority of animals (n = 6) exhibited moderate endometrial edema. Some animals (n = 2) showed extensive damage, with absence of luminal epithelium, extensive stromal edema, thin or absent glandular epithe-

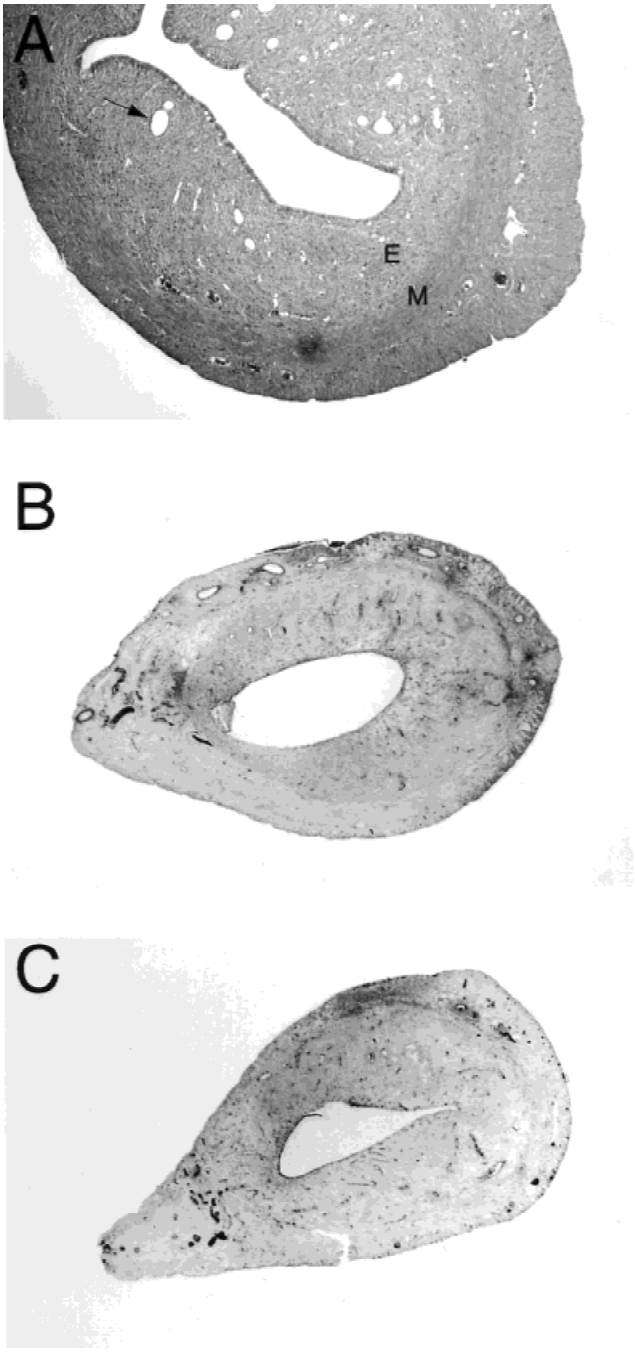

Fig. 2. Histology of cross sections of rat uterine horns after 1 hour of light irradiation. **A:** Vehicle-treated horn exposed to light from the nonlaser prototype shows normal endometrium (E) with glands (arrow) and myometrium (M). Necrosis of all layers of the uterine wall seen in uterine horns treated with 5-aminolevulinic acid and exposed to the nonlaser prototype (**B**) and to laser light irradiation (**C**). Magnification, 6.4×.

TABLE 1. Assessment of Uterine Horn Histology After Treatment With 5-Aminolevulinic Acid and 10 min of Light

	Number (cumulative) of animals exhibiting each finding			
	Luminal epithelium absent	Glandular epithelium absent	Stromal edema	Myometrium focally absent
Laser light (n = 4)	1	3	4	2
Prototype light (n = 4)	3	3	4	4

lium, and focal necrosis of the circular myometrium. In the laser treatment group, 1 hour of light exposure without ALA resulted in no histological damage in five animals and extensive damage to the uterine wall in two animals.

Table 1 summarizes the histologic changes observed in ALA-treated uterine horns exposed to 10 minutes of light treatment from both the laser and nonlaser prototype light sources. Endometrial glands were reduced in number and devoid of their epithelium in most of the specimens, and endometrial edema was observed in all specimens irrespective of the light source. Exposure to light from the nonlaser prototype light source resulted in consistent damage to the deepest layers of the uterine wall (Fig. 3). Exposure to laser light showed comparable full-thickness myometrial damage in two of the four treated animals. In the control group of animals not exposed to ALA (n = 7), 1 hour of light treatment from either laser or the nonlaser prototype light source did not result in any visible changes because the uterine histology was comparable to that of the contralateral horn (no light).

Temperature Results

The observed temperature increases, as measured by a thermocouple inside the uterine horn, are summarized in Figure 4. In the presence of ALA or vehicle alone, a similar temperature rise occurred during light irradiation when using either the prototype or laser source.

DISCUSSION

Different noncoherent light sources are being used in clinical and experimental PDT [15,24–26], mostly for the treatment of surface lesions. However, application of these light sources for treatment of hollow organs and cavities still represents a challenge because of the difficulty of focusing sufficient light devoid of an infrared component into small-diameter optical fibers. Presence of infrared light not only makes it difficult to quantify the dose of light treatment but may also significantly increase heat generated during light irradiation, especially in cavities and organs, where the heat dissipation mechanisms may not be very efficient. In this study, we examined and compared histologic and thermal effects of irradiating rat uterine horns with either a laser or a nonlaser prototype lamp.

The extent of damage to the ALA-treated uterine horns was dependent on the duration of light treatment. Exposure of ALA-induced PpIX photoactivated uterine horns for 1 hour produced extensive destruction, and no difference was noted between the prototype or the laser. The nonphotosensitized vehicle-treated right horn of the same animal was initially designed to serve as a control. Unexpectedly, variable degrees of damage following light treatment were observed. Most animals in both the nonlaser prototype and the laser-treated groups showed moderate or no damage. However, extensive uterine tissue necrosis was demonstrated in four animals (laser treated n = 2, nonlaser treated n = 2). To explain these results, two possibilities were considered: (a) thermal damage due to light irradiation and (b) contamination of the vehicle-treated horn due to crossover of the ALA from the contralateral horn. It has been reported that photoirradiation with red light results in the production of hyperthermia, the degree of which depends on the power used and the characteristics of the exposed tissue [27]. Although it is believed that mild tissue hyperthermia may contribute to the therapeutic effect of photodynamic therapy [28,29], excessive tissue heating could cause thermal damage not related to the photodynamic process. The possibility that ALA may have diffused from its site of injection or spilled from the distal portion of the horn or the cervix into the contralateral horn was also considered. Such diffusion probably did not occur in the current study because injection of methylene blue dye into one horn did not cause staining of the contralateral horn [30]. However, some ALA or PpIX may have entered into the lym-

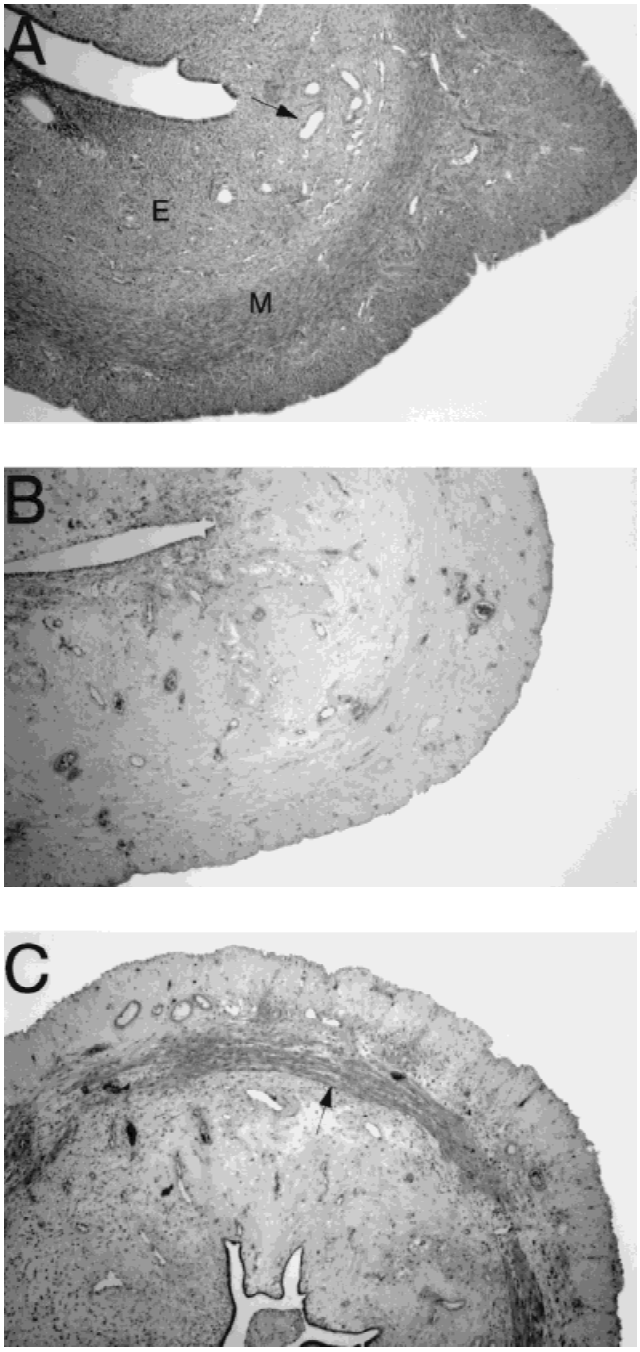

Fig. 3. Histology of cross sections of rat uterine horns. **A:** Normal uterine wall histology in the control horn (vehicle, no light) endometrium (E) with healthy glands (arrow) and myometrium (M). **B:** Complete necrosis of all layers of the uterine wall in a uterine horn treated with 5-aminolevulinic acid (ALA) and exposed to 10 minutes of light from the nonlaser prototype. **C:** Uterine horn treated with ALA and exposed to 10 minutes of laser light shows complete necrosis of the endometrial layer but some healthy residual myometrium (arrow). Magnification, 20×.

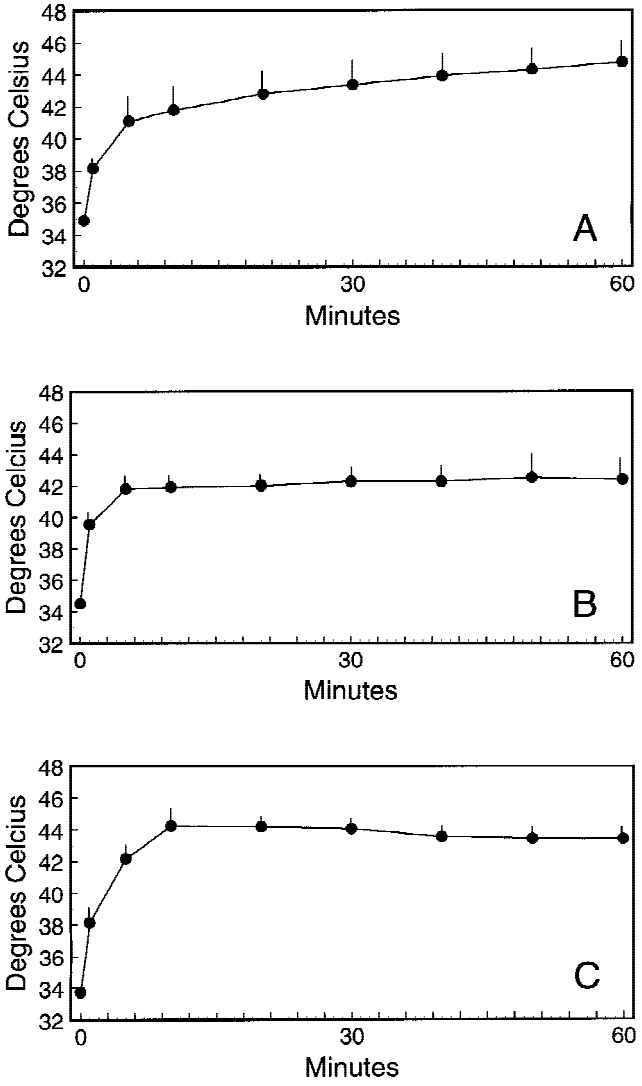

Fig. 4. Temperature monitoring during photoiradiation from the prototype or the laser of rat uterine horns with or without prior photosensitization with 5-aminolevulinic acid (ALA). Lines represent average values for the experiments. **A:** Prototype irradiation of ALA-exposed uterine horns (n = 4). **B:** Laser irradiation of ALA-exposed horns (n = 5). **C:** Prototype irradiation of control vehicle-treated horns (n = 5). Vertical lines through the data points indicate the standard error of the mean.

phatic system and the general circulation and thus was redistributed to the contralateral control horn [31]. Therefore, we included additional controls consisting of seven animals treated with vehicle only and exposed to the same duration of light treatment (1 hr). No change in uterine histology was observed, despite a high incident optical dose of 1,080 J/cm^2 in the laser- and the prototype-treated horns. Because exposure to light did not result in any histologic changes in the

uterine horns of animals not exposed to ALA, we concluded that contamination of the control horn with the ALA from the experimental horn, probably through lymphatics and general circulation, was responsible for the ablation seen in the control uterine horn.

Ten minutes of light exposure resulted in endometrial ablation that was comparable in both the laser- and prototype-treated groups. However, it is noteworthy that the destruction of the deepest layers of the uterine wall was more consistent with the nonlaser prototype. Although the duration of light treatment and the total power used were the same, the spectral properties of the two light sources were significantly different. The laser light consisted of narrow line emission at 630 nm, whereas the spectrum of the light emitted by the nonlaser prototype covered the range between 600 and 700 nm. Light in the vicinity of 630 nm has been the light of choice for ALA-based PDT because of the large absorption band for PpIX at 630–635 nm [32]. Although the ALA-induced PpIX in vivo absorbance maximum occurs at 635 nm, there is significant absorbance in the 620–640-nm range. Further, it is now known that, when PpIX is exposed to light, secondary PpIX-derived photoproducts are formed, of which photoprotoporphyrin is the major one [33,34]. Photoprotoporphyrin has an absorption peak at about 670 nm [32]. Use of the nonlaser prototype light source with an emission spectrum that covered the absorption spectrum of PpIX and its photoproducts could explain the results of better ablation seen in the deep layers of the uterine tissue after 10 minutes of light treatment. Differences in tissue penetrance of the wavelengths emitted by the laser and the nonlaser prototype also may have contributed to these results. The intensity of light propagation through the tissue decreases exponentially with distance from the source because of light scattering and absorption [35]. Because the absorption and scattering coefficients in tissue typically decrease with increasing wavelengths, longer wavelengths have greater tissue penetrance [36,37]. In vitro experiments using human uteri have demonstrated that penetration depth is increased significantly and can result in a 58–71% increase in fluence rate at a depth of 4 mm by increasing the wavelength from 630 to 690 nm [38].

Although there are significant animal-to-animal variations, it is quite clear that both light sources caused a similar temperature rise (average increase of ~10°C). Further, such increases were observed in the absence of ALA, indicating that the primary chromophore responsible for the observed temperature rise is not ALA-induced PpIX but rather other endogenous chromophores, possibly oxy- and deoxyhemoglobin.

In conclusion, we have shown that a prototype arc lamp achieved ablation of the rat endometrium that was comparable to that achieved with a laser. The temperature increase during treatment was also comparable for both light sources, suggesting that the reflective optics used in the design of the prototype excluded infrared contamination. More studies are needed to confirm the hypothesis that a nonlaser source may provide not only a less expensive but also a more effective approach to endometrial PDT.

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